

Chemical Specific Consultation
for
Perchlorate

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I. Background and Statement of Issues

The Superfund Site Assessment Branch (SSAB), Division of Health Assessment and Consultation, ATSDR, has requested that the Division of Toxicology, ATSDR, provide information on the current state of toxicological knowledge pertaining to perchlorate. The SSAB would also like recommendations for a health guidance value that could be used to evaluate the health threat posed by domestic use exposures to perchlorate in water from municipal supply wells.

This information will be shared with the California State Department of Health Services (DHS) and other parties addressing perchlorate contamination of groundwater at U.S. Environmental Protection Agency National Priority List (NPL) and other sites. In almost all cases, this perchlorate groundwater contamination has resulted from releases of rocket propellants that contain ammonium perchlorate. As a result of recent advances (April 1997) in the analytical detection capability by the California Department of Health Services for low concentrations of perchlorate (from 400 ppb down to 4 ppb), several water suppliers have detected perchlorate in drinking water wells and surface waters of southern California, Arizona, and Nevada (Mattie 1998). None of the documents reviewed by ATSDR indicate that perchlorate occurs naturally in groundwater.

II. Discussion

Perchloric acid and perchlorate salts contain chlorine in its highest (+7) oxidation state. When concentrated and heated or in the presence of reducing compounds, these chemicals are strong oxidizing agents (Cotton and Wilkinson 1988). However, in pure form and at room temperatures, they are stable. The perchlorate ion (ClO_4^-) is more stable than the ions of any of the other oxygen-containing acids of the halogens (Smith 1997).

Perchlorates are strong oxidizers and are used in pyrotechnics, matches, explosives, and jet and rocket fuels. They are also used as catalysts or digesting agents in analytical chemistry, in etching, engraving, and electroplating, and to generate oxygen in life-support systems in submarines, spaceships, and self-contained breathing apparatuses (US Army 1978). Perchlorate salts have anti-thyroid properties, and have been used to treat hyperthyroidism (Grave's Disease) and to stimulate the release of iodine from the thyroid gland in a diagnostic test of incorporation of iodine (Goodman et al. 1990). Sodium perchlorate is used as a nonspecific weed killer (Ellenhorn and Barceloux 1988).

ATSDR was unable to locate any documents summarizing the environmental chemistry of perchlorate or the other oxy-acids of chlorine, i.e. hypochlorite, chlorite, and chlorate. Likewise, there is no single document describing the pharmacodynamics, pharmacokinetics, and toxicology of these four compounds. These oxy-acids form salts with many bases, and each of these compounds will differ in its fate and effects in the environment and mammalian systems. This consultation addresses perchlorate only.

Most of the salts of perchloric acid are readily soluble in water. Thus, the perchlorate ion, regardless of its parent salt is mobile in soil, rapidly dispersed by water, and capable of migrating to groundwater. The perchlorate ion has been reported to be stable in tap water (Shigan 1963) and it may exist for many decades under typical groundwater and surface water conditions (Mattie 1998). The discussion below describes what is known about the toxicology of perchlorate. However, the data are not robust enough to evaluate the dose-response for thyroid effects or evaluate other potential target tissues or effects (Mattie 1998).

Clinical Effects - Acute Exposures

Inhalation. The vapor pressure of perchlorate salts and acids is expected to be low at normal temperatures. Thus, inhalation exposures to fumes or vapors would be negligible. Exposures to mists containing perchlorates or particulates onto which perchlorates have sorbed will produce symptoms such as upper respiratory tract irritation, sneezing, coughing, dyspnea (difficulty breathing), chest pain, and pulmonary edema. The onset of respiratory symptoms may be delayed for several hours (Von Burg 1995).

Direct Contact. Because perchlorates are strong oxidizers and water soluble, they are skin, eye, and mucous membrane irritants. Exposures to perchlorates in liquids, mists, or dusts will result in severe eye irritation characterized by lacrimation (tearing) and conjunctivitis (Von Burg 1995).

Ingestion. Clinical findings from studies of acute perchlorate ingestion exposures include nausea, vomiting, diarrhea, abdominal pain, hemolysis (destruction of red blood cells), cyanosis (deficient oxygenation causing purplish skin and mucous membranes), anuria (absence of urine formation), confusion, and convulsions (Meditext 1997). Irritation of the esophagus or gastrointestinal tract is predicted based on perchlorate's irritant properties (Meditext 1997). Perchlorate exposure may cause hemolysis with methemoglobin formation, disseminated intravascular coagulation, and nephrotoxicity (Meditext 1997). Coma and death can occur within a few hours of acute exposure as a result of either tissue hypoxia (deficiency in amount of oxygen reaching tissue; in this case from severe methemoglobinemia), hyperkalemia (greater than normal level of potassium circulating in blood) from massive hemolysis, or acute renal failure compounded by hemoglobinuria (presence of hemoglobin in blood plasma) (Ellenhorn and Barceloux 1988).

Clinical Effects - Chronic Exposures

Inhalation. Effects of longer term inhalation exposures are similar to those found with acute exposure (Jansen and Zeldenrust 1972).

Direct Contact. Effects of longer term direct contact exposures are similar to those found with acute exposure (Jansen and Zeldenrust 1972).

Ingestion. Chronic exposure to doses less than necessary to produce the symptoms described for

acute poisoning may lead to loss of appetite and weight loss (Dreisbach and Robertson 1987).

Epidemiological Studies

Rockette and Arena (1983) reviewed death certificates for workers known to have been exposed to perchloric acid, magnesium perchlorate, and other chemicals in a U.S. chemical plant. Because the workers had received multiple chemical exposures, the authors could not associate an elevated death rate for a particular time period or work area and a specific chemical.

Toxicological Studies - Humans

Most of the information in this section has been taken from a 1992 EPA document that described the derivation of a provisional Reference Dose (RfD) for perchlorates (EPA 1992).

Potassium perchlorate and, to a lesser extent, sodium perchlorate have been used orally to control Graves' Disease in humans. Symptoms of Graves' Disease include increased synthesis and secretion by the thyroid of iodide-containing hormones including triiodothyronine (T3) and tetraiodothyronine (T4 or thyroxine), thyroid gland enlargement, increased basal metabolism, and loss of weight. Perchlorate has been found to inhibit the synthesis and secretion of thyroid hormones by competitively inhibiting the accumulation of iodide in the thyroid (EPA 1992).

Normal production and secretion of thyroid hormones are controlled by iodide levels in the thyroid and by a feedback mechanism involving the production of thyroid stimulating hormone (TSH) by the anterior pituitary. TSH causes the thyroid to initiate new thyroid hormone synthesis. TSH production by the pituitary gland responds to blood levels of T3 and T4. When circulating levels of T3 and T4 decrease, the production of TSH in the pituitary increases. Conversely, increased levels of circulating T3 and T4 lead to decreased pituitary production of TSH (EPA 1992).

Physicians began treating Graves' Disease patients with perchlorate in the early 1950s when it was discovered that perchlorate both inhibited the uptake of iodine and stimulated its release by the thyroid in both humans and animals. Stanbury and Wyngaarden (1952) reported that 100 mg of potassium perchlorate administered orally one hour prior to administration of Iodine¹³¹ inhibited uptake into the thyroid for as long as six hours. Administration of 100 mg potassium perchlorate resulted in the nearly complete release, within 30 minutes, of previously accumulated I¹³¹ from the thyroids of Graves' Disease patients previously treated with tracer amounts of I¹³¹ and 1-methyl-2-mercaptimidazole (an antithyroid agent that inhibits the incorporation of iodide into thyroid hormone molecules). With smaller doses of potassium perchlorate, discharge of the I¹³¹ was incomplete. Wyngaarden et al. (1952, 1953) reported similar results with rats. In vitro studies of iodide transport in sheep thyroid tissue slices (Wolff and Maurey 1962) and phospholipid vesicles (Saito et al. 1983) have confirmed that perchlorate competitively inhibits iodide transport.

Perchlorate has been shown to produce effects on thyroid function in healthy humans that are similar to those seen in patients with hyperthyroidism. Burgi et al. (1974) reported that oral administration of 200 mg doses, three times daily for eight days significantly enhanced the secretion of non-thyroxine iodide from the thyroid in five healthy human volunteers. They also concluded that the data from their study and a previous study by Degroot and Buhler (1971) indicated that iodine uptake by the thyroid was completely blocked by this dosage of perchlorate.

The dosing regimen used in the early years of this practice consisted of repeated doses of 400-800 mg of perchlorate that were administered orally, usually in 200 mg doses two to four times daily to inhibit an overactive thyroid (Godley and Stanbury 1954). In later years, initial daily doses as high as 1600-2000 mg per day were administered, sometimes followed by daily maintenance doses of 200-800 mg per day (Crooks and Wayne 1960; Everd 1976).

The use of perchlorate to control excessive synthesis and release of thyroid hormones has caused skin rashes, sore throat, gastrointestinal irritation, and hematological side effects. Although early studies reported side effects to be reversible upon cessation of perchlorate administration, more widespread use of perchlorate revealed that hematological side effects were more severe and irreversible (EPA 1992).

Godley and Stanbury (1954) reported gastrointestinal irritation in two patients receiving 200 mg potassium perchlorate four times per day (800 mg total per day). Crooks and Wayne (1960) reported skin rash (six cases), nausea (five cases), and agranulocytosis (one case) among 75 patients receiving potassium perchlorate. Leucocyte counts returned to normal in the patient with agranulocytosis when potassium perchlorate administration (1500 mg per day) ceased. Morgans and Trotter (1960) reported that three percent of 180 patients treated with 400-1000 mg per day and eighteen percent of 67 patients treated with 1200-2000 mg per day of potassium perchlorate suffered from skin rashes, sore throats, and gastrointestinal irritation within two to three weeks of the commencement of treatment.

Between 1961 and 1966, the occurrence of hematological side effects led to the decreased use of perchlorate to treat hyperthyroidism (Everd 1976; Connell 1981). During this time, several cases of fatal aplastic anemia were reported in female patients receiving potassium perchlorate treatment for hyperthyroidism. The reported cases included a woman receiving 600 to 800 mg per day for 33 weeks (Hobson 1961), a woman treated for three months with 600-1000 mg per day (Johnson and Moore 1961), a woman treated with 400-600 mg per day for six months (Fawcett and Clark 1961), a woman treated with 450-800 mg per day for six months (Krevans et al. 1962), a woman receiving 400-600 mg per day for four to five months (Gjemdal 1963), and a woman receiving 1000 mg per day for two months (Barzilai and Sheinfeld 1966). A fatal case of agranulocytosis was reported in one woman treated with 1000 mg per day for a "few" months (Barzilai and Sheinfeld 1966) and other case reports describe non-fatal agranulocytosis in patients treated with 1000 mg per day for 12 days (Southwell and Randall 1960) or four months (Sunar 1963).

Fatal acute liver atrophy was reported for one patient who received 600 mg per day sodium perchlorate for 13 months (Kotzaurek 1965) and a nephrotic syndrome was reported for a patient treated with a total of 118 g of sodium perchlorate administered over a period of five months (Weber and Wolf 1969).

Toxicological Studies - Animal

Most of the information in this section has been taken from a 1992 EPA document that described the derivation of a provisional Reference Dose (RfD) for perchlorates (EPA 1992).

RTECS (1997) lists acute toxicity values for orally administered perchlorates originally published in the Russian scientific literature. Acute LD50 toxicity values for perchloric acid, sodium perchlorate, and potassium perchlorate are as follows: perchloric acid - 1100 mg/kg for rats and 400 mg/kg for dogs; sodium perchlorate - 2100 mg/kg for rats; ammonium perchlorate - 4200 mg/kg for rats, 1900 mg/kg for mice, 1900 mg/kg for rabbits, and 3310 mg/kg for guinea pigs. In rats, ammonium perchlorate is less toxic than sodium perchlorate, which is less toxic than perchloric acid.

The 1952 Wyngaarden study (Wyngaarden 1952) investigated anions that interfered with the accumulation and retention of iodide in the thyroid gland of the rat. Potassium perchlorate, which blocks transport of iodide into the thyroid, was administered in drinking water. Rats treated with an average dose of 2335 mg/kg/ day of perchlorate displayed enlarged thyroids, hyperplasia of the thyroid, decreased iodine concentrations in the thyroid, but no weight loss. Another group of rats was treated with propylthiouracil, which is believed to interfere with the incorporation of iodide into thyroid hormones. As with the perchlorate treated rats, the propylthiouracil treated rats displayed increased thyroid weight, hyperplasia of the thyroid, and decreased thyroid iodine content. However, the propylthiouracil treated rats also displayed decreased body weights throughout the treatment period.

Kessler and Kruskemper (1966) exposed rats to one percent potassium perchlorate in drinking water for up to two years. The EPA evaluated the results of this study and estimated an exposure dose of 1339 mg/kg/day (EPA 1992). Although body weights of control and treatment animals were comparable throughout the experiment, thyroid weights, both absolute and relative to body weight, were markedly increased in treated animals. Histological examination of thyroids from rats treated for 40 days revealed follicular cell hyperplasia with numerous cells in mitosis, colloid resorption, and low-grade mesenchymal reaction. The authors described the changes as typical for a thyroid gland stimulated by TSH for a relatively short period of time. After 200 days of perchlorate treatment, diffusely degenerative changes with fibrosis and increased colloid content in cells were noted. Four of the eleven rats treated with potassium perchlorate for two years displayed benign tumors of the thyroid gland; none of the 20 control animals displayed tumors (see discussion on carcinogenicity of perchlorates below).

Gauss (1972) exposed female mice to an estimated 2011 mg/kg/day dose of potassium

perchlorate (EPA 1992). Mice had ad libitum access to one percent potassium perchlorate for up to 160 days; exposures began when the mice were 50 to 60 days old. An 11.6 percent decrease in body weight was observed in the treated mice during the first two months of treatment; body weight data for longer treatment periods were not reported. Thyroid glands were examined histologically at 10 to 20 day intervals through 160 days. Thyroid volume, nuclei volume, and height of epithelial follicles were increased in treated mice throughout the treatment. A progressive change in the histological appearance of the thyroids of treated mice occurred, beginning with colloid loss, nuclei volume expansion, and increasing epithelium height that was followed by the appearance of hyperplasia and hypertrophy of the thyroid parenchyma. At later stages of the treatment period, hyperplastic follicles, areas of adenomatic tissue, adenoma complexes, and secreting cystadenomas were observed. However, No progression to malignancy was noted. Tumor incidence data were not reported.

Mannisto et al. (1979) evaluated the effects of potassium perchlorate and propylthiouracil on serum levels of TSH, T3, and T4 in rats. Potassium perchlorate concentrations of up to 500 mg/L (calculated dose of 76.3 mg/kg/day; 0.0305 L/day ingestion rate and 0.2 kg body weight for rats, EPA 1992) and propylthiouracil concentrations of up to 50 mg/L (calculated dose of 7.63 mg/kg/day; 0.0305 L/day ingestion rate and 0.2 kg body weight for rats, EPA 1992) were provided to mice in drinking water for four days. Potassium perchlorate in concentrations greater than or equal to 100 mg/L (15.3 mg/kg/day) and propylthiouracil in concentrations greater than or equal to 10 mg/L (1.53 mg/kg/day) both produced statistically significant increases in serum TSH levels and decreases in T3 and T4 levels. At 50 mg/L, potassium perchlorate significantly decreased levels of T3 and T4, but the increase in TSH was not statistically significant. At 10 mg/L, potassium perchlorate had essentially no effect on TSH, T3, or T4.

Hiasa et al.(1987) examined the effect of potassium perchlorate in the diet at 1000 ppm (80.7 mg/kg/day) and one-time injections of 28 mg/kg N-bis(2-hydroxypropyl)nitrosamine or DHPN, a demonstrated initiator of thyroid tumors that are promoted by propylthiouracil, on serum levels of T3, T4, and TSH. Radioimmunoassay techniques were used to assay the thyroid hormones. Both absolute and relative thyroid weights were significantly increased in perchlorate treated rats, with or without DHPN treatment. No effects were noted on body or liver weights. Serum levels of TSH were significantly increased in perchlorate treated rats with or without DHPN. Serum levels of T4 were decreased in perchlorate treated rats, but the decrease was statistically significant only in the DHPN plus perchlorate treated rats. Levels of T3 were comparable in perchlorate treated rats with or without DHPN. DHPN treatment alone produced no effects on body weight, thyroid weight, liver weight, or serum levels of TSH, T3, or T4. Thyroid tumors developed in 20/20 DHPN-perchlorate rats and in 1/20 in DHPN only rats. No thyroid tumors were observed in rats treated with perchlorate only. Follicular hyperplasia was noted in 1/20 rats treated with perchlorate only. Although diffused small follicles were also observed in the thyroids of these rats, the report did not specify the incidence of the nontumorous lesions.

Pajer and Kalisnik (1991) studied the effects of sodium perchlorate and gamma radiation on six

week old female mice. Mice were provided 1.2 percent sodium perchlorate (2147 mg/kg/day, water consumption rate - 0.0063 L/day, body weight - 0.0353 kg, EPA 1992) in drinking water for up to 46 weeks. At either week eight or week twelve of the experiment, some of the mice were irradiated with 0.8 Gy on five consecutive days at a dose rate of 1.45 Gy/minute of gamma rays for a total dose of 4 Gy. Thyroids and pituitaries of animals that survived the exposures (a total of 42) were histologically examined. Histological changes were noted in the thyroids and pituitaries, including thyroid follicular cell carcinoma. Incidences of follicular cell carcinoma were 0/22 in nonirradiated and irradiated control mice, 5/6 in perchlorate-nonirradiated mice and 14/14 in perchlorate-irradiated mice. No medullary carcinoma was found. Perchlorate treatment was associated with increased total volumes of the thyroid gland and distal parts of the anterior pituitary as well as increased average volumes and increased numbers of epithelial, thyrotropic and parafollicular cells.

Developmental and Reproductive Toxicity

Postel (1957) reported that the fetuses of pregnant rats exposed to 1% potassium perchlorate in drinking water from gestation day 21 through 48 displayed enlarged thyroids; however, the dams did not display enlarged thyroids as a result of the exposure. Maternal exposure to potassium perchlorate has been reported to produce endocrine abnormalities in rabbit, rat, and guinea pig fetuses (RTECS 1997). Chicks exposed to potassium perchlorate have demonstrated thyroid and other developmental abnormalities including reduced body weight gain, disturbed feather development, delayed and altered sexual development, and neurological disorders (Pflugfelder, 1959). Maternal exposure to potassium perchlorate has been reported to produce fetal and maternal hypothyroidism and goiters in rats (Lampe et al., 1967). Brown-Grant (1966) exposed pregnant Wistar rats to 1% potassium perchlorate in drinking water from gestation days 2 through 8. Although the fetuses were not examined for developmental effects, the author concluded that 1% potassium perchlorate in drinking water had no effect on the course of pregnancy in rats. Brown-Grant and Sherwood (1971) exposed pregnant Wistar rats that were also lactating to 1% potassium perchlorate or 0.1% potassium iodide using a similar protocol. However untreated controls were not included in the experiment. Exposure began on day 0 of pregnancy and continued until day 12 or 13. The number of implantation sites among treatments was comparable. Although relative thyroid weights in dams and offspring treated with perchlorate were increased over those in potassium iodide treated groups, the authors reported that the treatment with potassium perchlorate had no significant effect on blastocyst survival or the ability to implant while dams were lactating.

Genotoxicity

Although EPA (1992) and TERA (1997) reported that they could find no genotoxicity studies relevant to perchlorate carcinogenicity in the literature, Von Burg (1995) cited research (RTECS 1997) that found sodium perchlorate to affect DNA repair mechanisms in *E. coli*.

Pharmacokinetic Studies

Perchlorate appears to be eliminated from the body rapidly. Durand (1938) measured urinary elimination of perchlorate from two human subjects who ingested 0.784 g of sodium perchlorate in 100 g of water. Urinary elimination accounted for 50% of the administered dose within five hours and 95% within 48 hours.

Stanbury and Wyngaarden (1952) reported that perchlorate appears in the urine within 10-15 minutes of oral dosing with peak plasma levels occurring within three hours. Perchlorate was reported to undergo a two-phased urinary elimination process in rats and calves. In rats, the first phase accounted for approximately 96% of the administered dose and had a half-life of one to two hours. The second phase accounted for only 4% of the administered dose and had a half-life that ranged from 72-80 hours. In calves, the first phase half-life was reported to be 2-2.5 hours, and the second phase was 23-27 hours (Selivanova and Arefaeva 1986).

Goldman and Stanbury (1973) studied the pharmacokinetics of intraperitoneal injections of Cl^{36} -labeled potassium perchlorate in male Sprague-Dawley rats maintained on a low-iodine diet. Low levels of radiolabel were found in the thyroid. Peak concentrations of about 3.2% of dose per gram of thyroid were measured at about four hours. At 96 hours, the retention of label in the thyroid was higher than retention of label in the kidney, spleen, liver, or brain, but was less than 4% of the maximal levels measured at four hours. Most of the administered radiolabeled perchlorate was excreted in the urine.

AHFS (1984), EPA (1992), and Von Burg (1995) have all reported that perchlorate is not appreciably metabolized by the body before being rapidly excreted in the urine.

Carcinogenicity

Long-term interference of endocrine communication between the thyroid and pituitary glands appears to lead to thyroid follicular cell neoplasia. The information presented in the following paragraphs pertaining to perchlorate carcinogenicity have been taken from EPA (1992) and TERA Corporation (1997) reports.

TSH stimulates thyroid follicular cells to produce T3 and T4 and T3 and T4 inhibit synthesis of additional TSH. Thus high plasma levels of T3 and T4 reduce the amount of TSH produced and low levels increase the amount of TSH produced. If thyroid hormones are not produced in response to TSH, plasma levels of TSH remain elevated, resulting in a continual stimulation of the thyroid gland. The continual stimulation of the thyroid occurs any time this feedback mechanism is disrupted whether through iodine deficiency, thyroidectomy, or chemical disturbance.

The thyroid undergoes a series of morphological changes in response to long-term elevated TSH levels, regardless of the cause of the TSH elevation. Thyroid weight initially remains constant as

changes in thyroid morphology take place, including resorption of colloid from the follicular cell lumen and increases in cell volume and vascularity. Eventually, there is a rapid increase in thyroid weight and size as a result of follicular cell hyperplasia. Ultimately, the diffuse hyperplasia progresses to nodular proliferation of the follicular cells and eventually to benign and malignant tumors. The cellular progression occurs regardless of the cause of the thyroid insufficiency. Conditions that may cause this sequence of events include dietary iodine deficiency, blockage of iodine uptake into the thyroid, interference with thyroid hormone synthesis, suppression of thyroid activity by high concentration of iodine, enhanced metabolism of thyroid hormones, and damage to the thyroid gland.

TERA concluded that thyroid cancer induced by interference with thyroid-pituitary homeostasis is a threshold phenomenon (TERA 1997). TERA further cites the policy adopted by the EPA that assumes a threshold dose response for chemicals that cause a disruption of thyroid-pituitary homeostasis and have no genotoxic activity relevant to carcinogenicity. The EPA has cited the perchlorate ion as an example of a chemical known to disrupt thyroid-pituitary homeostasis by acting directly on the thyroid (EPA 1996).

In evaluating the carcinogenic potential of perchlorate, TERA cited two long-term studies of perchlorate in animals. Kessler and Kruskemper (1966) and Pajer and Kalisnik (1991) demonstrated that perchlorate induces follicular cell carcinogenesis. Shorter-term studies by Gauss (1972) and Hiasa et al. (1987) indicate that carcinogenesis is preceded by morphological changes typical of the pathological progression induced by TSH stimulation described by Hill et al. (1989).

The EPA has evaluated the potassium and sodium salts of perchlorate for carcinogenicity and has assigned them both a weight-of-evidence classification of B2, probable human carcinogen. However, because of the inadequacies of the toxicological data base for perchlorate, EPA has not developed a quantitative estimate of perchlorate carcinogenicity (EPA 1992). The National Toxicology Program of the U.S. Department of Health and Human Services has not conducted any carcinogenicity studies of perchlorate (NTP 1998).

Health Guidance Values

ATSDR is aware of several efforts to develop health guidance values for perchlorate. Differences of four orders of magnitude in the RfD values for noncancer endpoints result from selecting different NOAEL and LOAEL values and different uncertainty or modifying factors (see Table 1). Efforts to address cancer endpoints by the various groups developing guidance values are discussed below.

In 1992, the EPA developed a provisional RfD of 0.0001 mg/kg/day for potassium perchlorate (EPA 1992). However, EPA described its confidence in this provisional RfD as low because of limited availability of data on long-term, low-level exposure to potassium perchlorate. Although EPA did not develop a quantitative risk estimate for perchlorate carcinogenicity because of the

limitations of the data base, they did assign a weight-of-evidence classification of B2, probable human carcinogen to sodium and potassium perchlorates. EPA concluded that the classification for the two perchlorate salts was appropriate because the mechanisms of action on the thyroid were judged to be similar. EPA limited the cancer classification to these two salts since no data were available for other perchlorate compounds. EPA's decision not to develop a quantitative cancer estimate was based on inadequacies in studies in which tumors were observed that included small numbers of animals, use of single dose levels, lack of consumption data and high mortality and the hypothesis that there is a threshold for the carcinogenic effect for which linear extrapolation to estimate low dose risk would be inappropriate. EPA also cited the lack of genotoxicity data and lack of information on the potential for perchlorate to cause cancer at sites other than the thyroid or pituitary as reasons for not deriving a quantitative cancer estimate.

In 1995, the Perchlorate Study Group, a consortium of companies that use or manufacture perchlorates, conducted an extensive literature review to identify No Observed Adverse Effect Levels (NOAEL) and Lowest Observed Adverse Effect Levels (LOAEL) for perchlorates (Perchlorate Study Group 1995). They derived an RfD of 1.2 mg/kg/day. The EPA evaluated the Perchlorate Study Group literature review and concluded that the RfD of 0.0001 mg/kg/day was still appropriate. During the review, some EPA reviewers felt that an uncertainty factor of 10 for databases may not be required. Thus, the EPA also calculated an RfD using a safety factor of 3 and concluded that an RfD range of 0.0001 to 0.0005 mg/kg/day was appropriate until additional data were available (EPA 1995).

In 1996, the Aerojet General Corporation described "alternative approaches" to developing an RfD of 0.12 mg/kg/day and recommended a safe level for perchlorate in groundwater of 4 mg/L (Aerojet General Corporation 1996).

In 1997, The TERA Corporation developed a proposed RfD of 0.014 mg/kg/day for perchlorate (TERA 1997) for the Perchlorate Study Group. As with other efforts to develop a provisional RfD, confidence in the RfD was medium-to-low because of the general lack of information on the effects of chronic exposure to low doses of perchlorate. Because the RfD they developed would protect against disruption of the thyroid-pituitary homeostasis, TERA stated that the RfD should protect against both noncancer and cancer effects of perchlorate.

Provisional health guidance values that have been derived from the above studies (along with other information relevant to the derivation of these values) are presented in the accompanying table.

Provisional Health Guidance Values				
Group Deriving Value/Date (See References for specific citation)	Guidance Value mg/kg/day	Toxicological Effect Level & Effect	Uncertainty Factors	Confidence in Data Base
EPA 1992	RfD 0.0001 Ingestion	0.14 mg/kg single dose-acute human LOAEL (Stanbury and Wyngaarden 1952)- Iodine uptake by thyroid inhibited in humans	10-less than chronic study 10-protect sensitive individual 10-data base deficiencies 1000 total	Low
Perchlorate Study Group 1995	RfD 1.2 Ingestion	12 mg/kg/day subchronic human NOAEL/LOAEL (Brabant 1992, 1994, 1995)- perturbation of thyroid-pituitary axis in humans	3-less than chronic study 3-protect sensitive individual 9 total	No uncertainty factor for deficient data base recommended
EPA 1995	RfD 0.0001-0.0005 Ingestion	0.14 mg/kg* single dose-acute human LOAEL (Stanbury and Wyngaarden 1952)- Iodine uptake by thyroid inhibited in humans	10-less than chronic study 10-protect sensitive individual 10-data base deficiencies 1000 total 10-less than chronic study 10-protect sensitive individual 3- data base deficiencies 300 total	Uncertainty factor of 10 or 3 for deficient data base recommended
Aerojet 1996	RfD 0.12 Ingestion	12 mg/kg/day subchronic human NOAEL/LOAEL (Brabant 1994)-- perturbation of thyroid-pituitary axis in humans	10-less than chronic study 10-protect sensitive individual 100 total	No uncertainty factor for deficient data base recommended
TERA 1997 (for Perchlorate Study Group)	RfD 0.014 Ingestion	1.4 mg/kg/day single dose-acute human LOAEL (Stanbury and Wyngaarden 1952)- Iodine uptake by thyroid inhibited in humans	3-less than chronic study 3-protect sensitive individual 3-data base deficiency 3-extrapolate from a LOAEL to NOAEL 81 (100) total	Medium-to-low Uncertainty factor of 3 for deficient data base recommended

The data in Table 1 reveal a range of four orders of magnitude for perchlorate RfDs.

On March 6-7, 1997, an International Toxicity Estimates for Risk (ITER 1997a) Peer Review Panel concluded that the database for perchlorate was insufficient for development of an RfD. The Review Panel recommended that additional studies be conducted. As a result of this recommendation, the Perchlorate Study Group and the U.S. Air Force obtained funding to conduct additional studies. Another meeting of the ITER Panel was held on May 20, 1997 (ITER 1997b) to develop a list of priorities for further toxicological research that would permit the development of an RfD.

The recommended studies are summarized below; some modification of the protocols may occur when the actual studies are implemented. Ammonium perchlorate in drinking water is proposed to be used in all studies. This recommendation assumes that the ammonium ion will remain stable and not oxidize to nitrate.

Neurobehavioral Developmental Study - To address scientific uncertainties about the potential for perchlorate to cause neurobehavioral deficits due to toxicity to the developing thyroid, a rat study was proposed in which doses of 10.0, 3.0, 1.0, 0.1, and 0 mg/kg/day will be administered at confirmed day one of pregnancy through postnatal day 10. Learning tests will be administered to offspring at weanling and adult developmental stages. The purpose of this test is to provide better understanding of potential perchlorate effects on learning in human infants.

90-day Study - To address uncertainties about the critical effect of perchlorate exposure, a rat study was proposed in which doses of 10.0, 1.0, 0.2, 0.05, 0.01, and 0 mg/kg/day of perchlorate would be administered. Rats will be killed at 14 days for measurement of thyroid parameters, based on the hypothesis that most toxicity to the thyroid is seen during this time period. Additional rats will be treated for 90 more days at dose levels of 10, 1, 0.05, and 0 mg/kg/day with further maintenance without exposure for 30 days to determine whether there is any recovery from toxic effects seen at 90 days. Thyroid parameters will be measured at 14, 90, and 120 days along with clinical chemistry and hematological evaluations which will be performed at 45 and 90 days. Organ weights and histopathology will be evaluated at 90 days and at the end of the recovery period. Control and high dose groups will be evaluated; if pathological effects attributed to ammonium perchlorate are observed, the remaining dose groups will be evaluated. Immunotoxicity will be assessed at day 90 by measuring response in the sheep red blood cell assay (see discussion below). A dominant lethal assay also will be conducted at 90 days (see discussion below).

Literature Review of Receptor Kinetics Studies - The Peer Review Panel recommended a review of the literature pertaining to perchlorate discharge tests in humans and animals. If additional information is needed, additional studies could be performed.

Developmental Studies - The current data base is deficient with respect to effect of perchlorate exposure on skeletal development. If an evaluation of skeletal effects is not done as part of the Neurobehavioral Developmental study described above, a teratogenicity study in rats was recommended.

Absorption, Distribution, Metabolism, and Elimination Study - To aid in extrapolating across species and in selecting the most appropriate uncertainty factor to account for that extrapolation during RfD development, tissue uptake rates, serum half-lives, metabolic products, and radiolabelled perchlorate excretion should be measured in rats. The panel noted that this information would provide insight into the pharmacokinetics (movement of chemicals in biological systems as affected by uptake, distribution, elimination, and biotransformation) of perchlorate, but not the pharmacodynamics (binding and interactions of pharmacologically active molecules at their tissue sites of action).

Mutagenicity/Genotoxicity Study - To address in vivo genotoxicity of perchlorate, a dominant lethal test should be conducted at the end of the 90 day study. These tests are usually conducted in rodents with males being exposed to a single dose of the test compound and then mated to untreated females weekly for eight weeks. The females are killed before term and the number of corpora lutea determined. A separate bacterial mutagenicity (Ames) test of perchlorate is recommended to assess the potential for base-pair and frameshift mutations. A base-pair mutation occurs when one base-pair in DNA is replaced by another (e.g. guanine and cytosine are replaced by adenine and thymine). The consequences of a base pair substitution depend on whether the mutation is a missense or nonsense mutation. In a missense mutation, there is a change in the code for one amino acid to that for another. The mutation can inactivate the gene product, have only a slight effect on function, or be virtually without effect, depending on the specific amino acid substitution and its specific position within the gene product. In a nonsense mutation, the gene product is incomplete and nonfunctional because of premature termination of protein synthesis. Mutations that alter the reading frame of the genetic code are called frameshift mutations. Most commonly, frameshift mutations involve the gain or loss of one or two base pairs in a gene. The gene product is grossly altered because of the change in reading frame. The gene product is apt to be incomplete because the new reading frame is likely to include a nonsense codon which specifies no amino acid at all. Frameshift mutations therefore lead to nonfunctional gene products.

Reproductive Study - A two generation reproductive study should be considered once the results of the 90-day and neurobehavioral studies are available.

Immunotoxicity Study - A humoral immunity study using sheep red blood cells is part of the 90-day study. In this study, sheep red blood cells will be used in a rodent study as an antigenic challenge after exposure to perchlorate. The immune response in such studies is usually quantitated either by measuring the serum antibody titers or by determining the number of splenic lymphocytes producing antibody to the specific eliciting antigen. Other immunotoxicity assays should be considered after the results of the 90-day and neurobehavioral studies are

available.

Other Studies - In addition to these studies, the ITER Peer Review Panel recommended that an in-depth review of the current literature on the toxicity of perchlorate compounds and on the comparative sensitivity of humans and rats to thyroid toxicants be conducted. The ITER Peer Review Panel has stated that it is essential to complete the neurobehavioral developmental and 90-day studies to determine if the critical effects of perchlorate have been identified. The remaining studies are recommended to address remaining uncertainties in the data base. No studies are included in this battery of tests to specifically evaluate the carcinogenic potential of perchlorate. As previously stated, the National Toxicology Program of the U.S. Department of Health and Human Services has not conducted any carcinogenicity studies of perchlorate (NTP 1998).

In addition to health effects research, research is currently underway to refine analytical techniques and ascertain the nature and extent of perchlorate contamination. Research is also being conducted to study the environmental fate and transport and ecological impacts of perchlorate (Mattie 1998).

Interagency Perchlorate Steering Committee

An Interagency Perchlorate Steering Committee (IPSC) was formed in January 1998 to bring together government representatives from the Environmental Protection Agency, Department of Defense, Agency for Toxic Substances and Disease Registry, National Institute for Environmental Health Sciences, and affected states and local governments. Participation in the IPSC has also been solicited from the Department of the Interior, Bureau of Water Reclamation, the Colorado River Nations Alliance, and the Native American Consult. The charter is intended to facilitate and coordinate accurate accounts of related technological issues and to create information transfer links for interagency and intergovernmental activities regarding these areas of concern (Mattie 1998). Monthly teleconferences are held to update participants on events and breaking news regarding controversial or technological issues. Public meetings will be held to distribute the most current scientific information on the key issues and to hear stakeholder and public concerns. Fact sheets are being made available for public distribution (Mattie 1998). The IPSC will greatly facilitate the proposed research effort and will be a forum for ensuring that state-of-the-science efforts are brought to bear on addressing the unique issues of perchlorate contamination.

Future Actions

The National Center for Environmental Assessment in the Office of Research and Development of the Environmental Protection Agency plans to evaluate the perchlorate assessment generated by the ongoing research at the end of September 1998. The new assessment, all of the new data, and the study protocols will be subjected to an external peer review in October 1998 before the assessment is finalized (Mattie 1998). The Environmental Protection Agency Office of Water

may develop regulatory standards for perchlorate in the future. Perchlorate has been included on the Contaminant Candidate List by the Environmental Protection Agency. In accordance with the 1996 amendments to the Safe Drinking Water Act, the Environmental Protection Agency is required to develop a list of contaminants that are potential candidates for future drinking water research, guidance development, and future regulation, if necessary. At this time, the Contaminant Candidate List notes that additional data on health effects, occurrence, analytical methods, and treatment technologies are needed for perchlorate before decisions can be made to regulate, develop guidance and/or a health advisory, or do nothing (Mattie 1998).

Toxicological Profile Development

ATSDR has not prepared a Toxicological Profile for perchlorate and therefore has not developed a Minimal Risk Level (MRL) for it. However, perchlorate is currently being considered for profile development. The research proposed above will likely provide the information needed for ATSDR to develop an MRL.

III. Conclusions

1. Provisional Reference Doses (RfDs) developed for perchlorate by various groups span four orders of magnitude because of the use of different NOAEL and LOAEL values and different uncertainty factors.
2. The toxicological data base for perchlorate is incomplete. The lack of toxicological information has hampered efforts to develop a definitive health guidance value. The variability of the provisional RfDs that have been developed has been caused by disagreements in the quality and different interpretations of the toxicological data base.
3. The Perchlorate Study Group and the U.S. Air Force have obtained funding to conduct additional toxicological studies on perchlorate. An International Toxicity Estimates for Risk (ITER) Peer Review Panel (ITER 1997b) has developed a list of toxicological studies (discussed above) and assigned priorities for completing each study. An Interagency Perchlorate Steering Committee has been established to facilitate and coordinate accurate accounts of related technological issues and to create information transfer links for interagency and intergovernmental activities.
4. ATSDR has not prepared a Toxicological Profile or Minimal Risk Level for perchlorate. However, ATSDR is currently considering perchlorate as a candidate for profile development. There has been no single definitive review of the health effects of the other salts of oxy- acids of chlorine, i.e. hypochlorite, chlorite, and chlorate and this consultation pertains to perchlorate only. The potential exists for perchlorates and the other oxy- acids of chlorine to have toxic effects other than those noted for the thyroid and pituitary glands.
5. The studies proposed by the ITER Peer Review Panel (ITER 1997b) and discussed above

should provide the toxicological information needed to develop a definitive health guidance value for perchlorate. Additional information may be needed on the carcinogenic potential of perchlorate.

6. Additional information pertaining to the environmental chemistry, pharmacokinetics, and pharmacodynamics of hypochlorite, chlorite, chlorate, and perchlorate would be useful in evaluating the potential health effects associated with environmental exposures to these compounds.

7. The provisional RfD range developed by EPA is 0.0001 to 0.0005 mg/kg/day. This range would result in safe drinking water values of 0.001 to 0.005 mg/L for a 10 kg child ingesting one liter of water per day and 0.0045 to 0.0175 mg/L for a 70 kg adult ingesting two liters of water per day.

IV. Recommendations

1. ATSDR should remain active in the Interagency Perchlorate Steering Committee and obtain and review the results of toxicological studies conducted on perchlorate.

2. ATSDR should consider perchlorate a candidate for a Toxicological Profile and develop a Minimal Risk Level (MRL) as soon as the toxicological data base is adequate. ATSDR may want to consider including the salts of the other oxy- acids of chlorine, i.e. hypochlorite, chlorite, and chlorates.

3. ATSDR should consider supporting efforts to gather information related to the environmental chemistry of perchlorate and other oxy-acids of chlorine in the environment and the pharmacokinetics and pharmacodynamics of perchlorate and other oxy-acids of chlorine in mammalian systems.

3. Because ATSDR's assumptions and methods for developing MRLs are most similar to the methods used by EPA to develop RfDs, the provisional RfD range of 0.0001 to 0.0005 mg/kg/day developed by EPA appears to be the most appropriate provisional health guidance value to use in evaluating ingestion exposures to perchlorate until the EPA can develop a definitive RfD and ATSDR can develop an MRL. Until a definitive health guidance value is developed, this provision RfD range should be used with caution and site-specific issues should be considered in all cases.

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PERCHLORATE FACT SHEET

The Division of Toxicology of ATSDR has prepared this fact sheet to summarize the current state of toxicological knowledge pertaining to perchlorates.

Perchlorates are oxygen containing acids of chlorine that contain chlorine in its highest (+7) oxidation state. Although perchlorates in pure form are stable at room temperatures, they are potent oxidizers and are used in fireworks, matches, explosives, and jet and rocket fuels.

Health effects that may occur as a result of acute exposures include the following: upper respiratory tract irritation, sneezing, coughing, difficulty breathing and chest pain with inhalation exposures to perchlorate containing mists or particulates; skin, eye, and mucous membrane irritation with direct contact exposures to perchlorates in liquid form or in mists or particulates; nausea, vomiting diarrhea, abdominal pain, cyanosis (deficient oxygenation causing purplish skin and mucous membranes), absence of urine formation, confusion, and convulsions with ingestion exposure. Health effects seen with chronic exposures are similar to those seen with acute exposures but may also include loss of appetite and weight loss.

Perchlorates may cause hemolysis (breakdown of blood cells) which may lead to hemoglobinuria (presence of hemoglobin in the urine), disseminated intravascular coagulation (clotting of blood in small blood vessels), and nephrotoxicity (kidney toxicity). Disseminated intravascular coagulation and formation of methemoglobin (oxidized hemoglobin that is incapable of reversibly binding to oxygen) may lead to tissue hypoxia (deficiency of oxygen reaching tissues), and acute kidney failure which can lead to coma and death within a few hours.

The potassium and sodium salts of perchlorate have been used in the treatment of hyperthyroidism. Normal production and secretion of thyroid hormones (triiodothyronine or T₃ and tetraiodothyronine or T₄) are controlled by iodide levels in the thyroid and by a feedback mechanism involving the production of thyroid stimulating hormone (TSH) by the anterior pituitary. TSH causes the thyroid to initiate new thyroid hormone synthesis. TSH production by the pituitary gland responds to blood levels of thyroid hormones. When circulating levels of thyroid hormones decrease, the production of TSH in the pituitary increases. Conversely, increased levels of circulating thyroid hormones lead to decreased pituitary production of TSH. Hyperthyroidism or Grave's Disease is a condition where the thyroid synthesized and secretes excessive amounts of thyroid hormones. In the early 1950s, physicians began treating Grave's Disease patients with perchlorate when it was discovered that perchlorate would control excessive synthesis and release of thyroid hormones. The use of perchlorate to treat Grave's Disease has been associated with skin rashes, sore throat, and gastrointestinal irritation. Use of perchlorate to treat Grave's Disease was discontinued in the 1960s when aplastic anemia and other irreversible hematological side effects were observed in treated patients.

The toxicological data base for perchlorate is incomplete. Efforts to develop health guidance

values that can be used to evaluate exposures have resulted in different values because of the use of different Lowest Observed Adverse Effect Levels (LOAELs) and No Observed Adverse Effect Levels (NOAELs) and different uncertainty and modifying factors. The range of Provisional Reference Doses (RfDs; a Reference Dose is an estimate, with uncertainty spanning perhaps an order of magnitude, of a daily exposure to the human population, including sensitive subgroups, that is likely to be without an appreciable risk of deleterious effects during a lifetime) developed by various groups is 0.0001 to 1.2 mg/kg/day. The U.S. Environmental Protection Agency (EPA) has developed the most conservative reference dose range of 0.0001 to 0.0005 mg/kg/day which yields safe drinking water values for perchlorate of 0.001 to 0.005 mg/L for a 10 kg child ingesting one liter of water per day and 0.0045 to 0.0175 mg/L for a 70 kg adult ingesting two liters of water per day.

The EPA has evaluated the potassium and sodium salts of perchlorate for carcinogenicity and has assigned them both a weight-of-evidence classification of B2, probable human carcinogen. However, because of the inadequacies of the toxicological data base for perchlorate, EPA has not developed a quantitative estimate of perchlorate carcinogenicity.

Research is currently under way to fill the data gaps in the toxicological data base for perchlorate. Proposed research includes neurobehavioral, developmental, pharmacokinetic, genotoxic, reproductive, immunotoxic, and 90-day toxicological studies.

Although ATSDR has not developed a Toxicological Profile or Minimal Risk Level (MRL; a Minimal Risk Level is an estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure) for it, perchlorate is currently under consideration.

Anyone having questions about perchlorate toxicity should call the Division of Toxicology of ATSDR at 404/639-6300.